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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/769,107 | 01/24/2001 | Vincent P. Sandanayaka | WYTH0144-100/AM100182 01 | 4495 |

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|---|---|
| COVINGTON, RAYMOND K | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1625 | |

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/769,107 | SANDANAYAKA ET AL. | |
| | Examiner | Art Unit | |
| | Raymond Covington | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14,29-31,33-39,45-49 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,29-31,33-39,45-49 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-14, 29-31 and 33-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Kende et al J. Org. Chem. Vol. 55 pp.1125-1126. Kende et al teach a method of making alpha sulfone ester derivative as recited in the claims. See page 1125, scheme I and Table 1.

Claims 1-14, 29-31, 33-39, 45-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Levin et al WO 00/44723. Levin et al teach a method of making alpha sulfone ester derivative as recited in the claims. See, for example, page 66, example 24 corresponding to compounds where Z is ethyl and page 68 example 25 where Z is chlorobenzyl.

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 29-31, 33-39, 45-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-14, 29-31, 33-39, 45-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling compounds of formula I, V and IX where **$R_1$ $R_2$ taken together with the carbon atom to which they are attached form a piperidine ring, Z is $CH_3$-$CH_2$-O-, OH-NH-, OH or $CH_3$-O-, and $R_3$ is a phenyl group, does not reasonably provide enablement for the broader scope in claims dependent thereon.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Specification provides no guidance as to what other rings, for example, might be

suitable and there is no basis in the prior art directed to similar compounds having the same activity as herein.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art;

All of the factors have been considered but only the most relevant will be discussed below.

1) the nature of the invention;

The claims are drawn to alpha-sulfonyl compounds and processes for making these compounds having substituents $\mathbf{R_1}$ $\mathbf{R_2}$ form R1 and R2 taken together with the carbon atom to which they are attached form a 5-10 membered cycloheteroalkyl ring containing 1-3 heteroatoms selected from the group consisting of N, NK, O and S; and the cycloheteroalkyl may be optionally substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to

3 triple bonds, cycloalkyl of 3-6 carbon atoms, -$OR_5$ ,=O, -CN, -$COR_5$. perfluoroalkyl of 1-4 carbon atoms, -o-perfluoroalkyl of 1-4 carbons atoms, -$CONR_5R_6$, -$S(O)_nR_5$, -$OPO(OR_5)OR_6$, -$PO(OR_5)R_6$, .- $OC(O)OR_5$, -$OR_5NR_5R_6$, - $OC(O)NR_5R_6$, -$C(O)NR_5OR_6$, -$COOR_5$, -$SO_3H$, -$NR_5R6$, -$N((CH_2)_2)_2NR_5$, - $NR_5COR_6$, -$NR_5COOR_6$, $SO_2NR_5R_6$, -$NO_2$, -$N(R_5)SO_2R_6$, -$NR_5CONR_5R_6$, - $NR_5C(=NRS)NR_5R_6$, -$NR_5C(=NR_6)N(SO_2R_5)R_6$, - $NR_5C(=NR_6)N(C=OR_5R_6$, tetrazol-s-yl, -$SO_2NHCN$, -$SO_2NHCONR_5R_6$, phenyl, heteroaryl, cycloalkyl and 5-10 membered cycloheteroalkyl , **Z** being Z is H, OH, -NYOX, -$OR_5$ or – $NR_5R_6$, $\mathbf{R_3}$ is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5- 10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_4$, O, and S

2) the breadth of the claims;

A review of the specification shows no compounds described that are representative of actual working examples other than where $\mathbf{R_1}$ $\mathbf{R_2}$ **taken together with the carbon atom to which they are attached form a piperidine ring, Z is $CH_3$-$CH_2$-O-, OH-NH-, OH or $CH_3$-O-, and $R_3$ is a**

**phenyl group** with no examples showing how to make or use compounds having heteroaryl substituents, for example.

3) the predictability or unpredictability of the art;

There is thus no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and further would not be produced by the same process. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

the amount of direction or guidance presented;

There is insufficient disclosure of starting materials that would place such a diverse genus of compounds in possession of the public in the event of a patent grant.

4) the presence or absence of working examples;

The limited number of examples do not enable the preparation of such a diverse group the compounds embraced by the claims as presently recited.

5) the quantity of experimentation necessary;

There is insufficient disclosure of starting materials that would place such a diverse genus of compounds in possession of the public in the event of a patent grant. In addition, there is no reasonable assurance that such an alleged genus

of compounds could be made by the same process. See In re Fouche 169 USPQ 429 ((CCPA 1971)). This is particularly true where large groups such as heteroaryl may sterically hinder or may prevent the making of the starting materials, intermediates or final products.

6) the state of the prior art; and,

Applicants are claiming, for example, heterocyclic substituted compounds. Applicants have not disclosed any working examples, which would demonstrate, or guide, one skilled in the art as to how the heterocyclic substituted or other substituent groups other than where **$R_1$ $R_2$ taken together with the carbon atom to which they are attached form a piperidine ring, Z is $CH_3$-$CH_2$-O-, OH-NH-, OH or $CH_3$-O-, and $R_3$ is a phenyl group** were prepared or obtained. The process of making the recited compounds is not readily apparent from the specification. The specification must teach how to make the invention. *In re Gardner*, 166 U.S.P.Q. 138 (1970). In order to practice the claimed invention, one skilled in the art would have speculate how the derivatives were obtained or prepared.

7) the relative skill of those skilled in the art;

The level of skill in art is high.

In consideration of each of factors 1 – 8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim 46 is rejected to the extent it reads on and depends from a rejected base claim.

Claims 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for treating any disease or condition. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The [eight] factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*,

230 USPQ 546. The main issues are the correlation between clinical efficacy and Applicants' In Vitro Gelatinase Assay, In Vitro Collagenase Assay and TACE Inhibition assays.

a) Determining if any particular claimed compound would treat a given disease or condition would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating a disease or condition is found in page 2 last paragraph and page 3 first paragraph of the specification, which merely states Applicants' intention to do so. Applicants describe formulations in page 23. Doses required to practice their invention are described in page 23, 4th full paragraph. A 1000-fold range of doses is recommended. Since no aplpha-sulfonyl compounds of the type recited in the claims has ever been used to treat any human disease or condition, how is the skilled physician to know what dose to use for each of these different diseases? There is an *in vitro* assay described in pages 73-75, but it is unclear if this assay is correlated with being effective for treatment of any disease or condition. c) There is no working example of treatment of any disease or condition in man or animals. The TACE assay provides evidence that the present compounds inhibit TNF-alpha

converting enzyme. However, inhibition does not equal treatment or prevention of any disease or condition. d) The nature of the invention is clinical treatment of disease with compounds of claim 1, which involves physiological activity. e) The state of the clinical arts involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. See, for example, Verdile et al Pharma. Res. Vol. 50 pp 397-409 (2004) in particular section 8 page 406, and Walsh et al BioChem. Soc Trans. Vol. 33 part 5 pp 1087-1090particularly page 1089 right column.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable

factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). h) The scope of the claims involves all of the varied of compounds of claim 1

Thus, the scope of claims is broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.

Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Additionally, with respect to claim 48, determining whether a given disease responds or not to such a mode of action involves much experimentation since a negative response from one patient does not mean the drug isn't useful as no drug has 100% effectiveness. Thus what "success rate" determines if a particular inhibitor is effective and how many patients (and dosage regimens) need to be tested? Further, defining a disease or condition by its (their) underlying cause renders the scope of intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood.

Additionally with respect to claims 49, there is no absolute predictability and no established correlation between in vitro activity and the treatment of viral conditions such as HIV as the in vitro data is not a reliable predictor of success even in view of the seemingly high level of skill in the art.

It is well known, for example, in the art that autoimmune disorders are composed of many different diseases including pneumonia, Kaposi's sarcoma, Epstein Barr virus and various other opportunistic diseases caused by fungi, viruses, bacteria and protozoans. See, for example, Acta Microbiol. Immun. Hung.

41(1), 5-21 (1994), Proc. Annu. Meet. Med. Sect. Am. Counc. Life Insurance, 41-52 (1993). The claim language, necessarily extends the treatment to complications against which the invented compounds (or compositions) have not been demonstrated to be effective.

In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would not recognize the nexus between the between in vitro activity and the particular respiratory disease to be treated. Neither does the instant specification adequately describe the nexus between the between in vitro activity and the treatment of autoimmune disorders.

The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated, prevented, ameliorated by the compounds of the instant claims, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 48 is unclear. Defining a disease by its (their) underlying cause renders the scope of intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond Covington whose telephone number is (571) 272-0681. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie at telephone number (571) 272-0681.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Thomas McKenzie
SPE
Art Unit 1625

RKC